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(54) Title: SUBSTITUTED IMIDAZOPYRIDINES

(57) Abstract: Imidazopyridine compounds that contain substituted amine functionality at the 1-position are useful as immune response modifiers. The compounds and compositions of the invention can induce the biosynthesis of various cytokines and are useful in the treatment of a variety of conditions including viral diseases and neoplastic diseases.

Substituted Imidazopyridines

Field of the Invention

This invention relates to imidazopyridine compounds that have substituted amine functionality at the 1-position, and to pharmaceutical compositions containing such compounds. A further aspect of this invention relates to the use of these compounds as immunomodulators, for inducing cytokine biosynthesis in animals, and in the treatment of diseases, including viral and neoplastic diseases.

Background of the Invention

The first reliable report on the 1*H*-imidazo[4,5-*c*]quinoline ring system, Backman et al., J. Org. Chem. 15, 1278-1284 (1950) describes the synthesis of 1-(6-methoxy-8-quinolinyl)-2-methyl-1*H*-imidazo[4,5-*c*]quinoline for possible use as an antimalarial agent. Subsequently, syntheses of various substituted 1*H*-imidazo[4,5-*c*] quinolines were reported. For example, Jain et al., J. Med. Chem. 11, pp. 87-92 (1968), synthesized the compound 1-[2-(4-piperidyl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline as a possible anticonvulsant and cardiovascular agent. Also, Baranov et al., Chem. Abs. 85, 94362 (1976), have reported several 2-oxoimidazo[4,5-*c*]quinolines, and Berenyi et al., J. Heterocyclic Chem. 18, 1537-1540 (1981), have reported certain 2-oxoimidazo[4,5-c]quinolines.

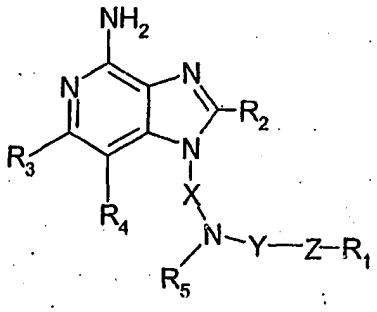
Certain 1*H*-imidazo[4,5-*c*]quinolin-4-amines and 1- and 2-substituted derivatives thereof were later found to be useful as antiviral agents, bronchodilators and immunomodulators. These are described in, *inter alia*, U.S. Patent Nos. 4,689,338; 4,698,348; 4,929,624; 5,037,986; 5,268,376; 5,346,905; and 5,389,640, all of which are incorporated herein by reference.

Substituted 1*H*-imidazopyridine-4-amine compounds useful as immune response modifiers are described in United States Patent Nos. 5,446,153; 5,494,916; and 5,644,063. The compounds described in these patents do not have amine containing substitution at the 1- position. Certain 1*H*-imidazo[4,5-*c*]quinolin-4-amines that have amide, sulfonamide, and urea functionality at the 1-position are described in PCT Publications WO 00/76505, WO 00/76518 and WO 00/76519.

Despite these recent discoveries of compounds that are useful as immune response modifiers, there is a continuing need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other mechanisms.

Summary of the Invention

We have found a new class of compounds that are useful in inducing cytokine biosynthesis in animals. Accordingly, this invention provides imidazopyridine-4-amine compounds that have a substituted amine functionality at the 1-position. The compounds which have been found to be useful inducers of cytokine biosynthesis are defined by Formula (I), which is described in more detail *infra*. Formula (I) is as follows:



(I)

wherein X, Y, Z, R_1, R_2, R_3, R_4, and R_5 are as defined herein.

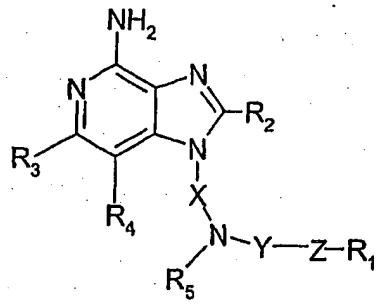
The compounds of Formula (I) are useful as immune response modifiers due to their ability to induce cytokine biosynthesis and otherwise modulate the immune response when administered to animals. This makes the compounds useful in the treatment of a variety of conditions such as viral diseases and tumors that are responsive to such changes in the immune response.

The invention further provides pharmaceutical compositions containing the immune response modifying compounds, and methods of inducing cytokine biosynthesis in an animal, treating a viral infection in an animal, and/or treating a neoplastic disease in an animal by administering a compound of Formula (I) to the animal.

In addition, the invention provides methods of synthesizing the compounds of the invention and intermediates useful in the synthesis of these compounds.

Detailed Description of the Invention

As mentioned earlier, we have found that certain compounds induce cytokine biosynthesis and modify the immune response in animals. Such compounds are represented by Formula (I) below:



(I)

wherein **X** is alkylene or alkenylene;

Y is –CO–, –CS–, or $–SO_2–$;

Z is a bond, –O–, –S–, or $–NR_5–$;

$\mathbf{R_1}$ is aryl, heteroaryl, heterocyclyl, C_{1-20} alkyl or C_{2-20} alkenyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of:

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-substituted cycloalkyl;

-O-alkyl;

$-O-(alkyl)_{0-1}$-aryl;

$-O-(alkyl)_{0-1}$-heteroaryl;

$-O-(alkyl)_{0-1}$-heterocyclyl;

-COOH;

-CO-O-alkyl;

-CO-alkyl;

-$S(O)_{0-2}$-alkyl;

-$S(O)_{0-2}$–$(alkyl)_{0-1}$-aryl;

-$S(O)_{0-2}$–$(alkyl)_{0-1}$-heteroaryl;

-$S(O)_{0-2}$–$(alkyl)_{0-1}$-heterocyclyl;

-$(alkyl)_{0-1}$-$N(R_5)_2$;

-$(alkyl)_{0-1}$-NR_5-CO-O-alkyl;

-$(alkyl)_{0-1}$-NR_5-CO-alkyl;

-$(alkyl)_{0-1}$-NR_5-CO-aryl;

-$(alkyl)_{0-1}$-NR_5-CO-heteroaryl;

-N_3;

-halogen;

-haloalkyl;

-haloalkoxy;

-CO-haloalkyl;

-CO-haloalkoxy;

-NO_2;

-CN;

-OH;

-SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R_2 is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-alkyl-O-alkyl;

-alkyl-S-alkyl;

-alkyl-O-aryl;

-alkyl-S-aryl;

-alkyl-O- alkenyl;

-alkyl-S- alkenyl; and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;
-halogen;
-$N(R_5)_2$;
-$CO\text{-}N(R_5)_2$;
-$CS\text{-}N(R_5)_2$;
-$SO_2\text{-}N(R_5)_2$;
-$NR_5\text{-}CO\text{-}C_{1\text{-}10}$ alkyl;
-$NR_5\text{-}CS\text{-}C_{1\text{-}10}$ alkyl;
-$NR_5\text{-}SO_2\text{-}C_{1\text{-}10}$ alkyl;
-$CO\text{-}C_{1\text{-}10}$ alkyl;
-$CO\text{-}O\text{-}C_{1\text{-}10}$ alkyl;
-N_3;
-aryl;
-heteroaryl;
-heterocyclyl;
-CO-aryl; and
-CO-heteroaryl;

$\mathbf{R_3}$ and $\mathbf{R_4}$ are independently selected from the group consisting of alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio; and

each $\mathbf{R_5}$ is independently H or $C_{1\text{-}10}$ alkyl;

or a pharmaceutically acceptable salt thereof.

Preparation of the Compounds

Compounds of the invention can be prepared according to Reaction Scheme I where R_1, R_2, R_3, R_4, R_5, X, Y and Z are as defined above, Bn is benzyl and R' is alkyl of one to four carbon atoms, perfluoroalkyl of one to four carbon atoms, phenyl, or phenyl substituted by halogen or alkyl of one to four carbon atoms.

In step (1) of Reaction Scheme I a 3-nitropyridine-2,4-disulfonate of Formula X is reacted with an amine of Formula $R_1\text{-}Z\text{-}Y\text{-}N(R_5)\text{-}X\text{-}NH_2$ to provide a 3-nitro-4-aminopyridine-2-sulfonate of Formula XI. Due to the presence of two sulfonate groups that could in principle be displaced, the reaction may provide a mixture of products that can be readily separated using conventional techniques such as column chromatography.

The reaction is preferably carried out by adding the amine to a solution of a compound of Formula X in a suitable solvent such as dichloromethane in the presence of a tertiary amine such as triethylamine. As the sulfonate group is a relatively facile leaving group, the reaction can be run at a reduced temperature (0°C) in order to decrease the amount of undesired 2-aminated and 2,4-diaminated side products. 3-Nitropyridine-2,4-disulfonates are known and can be readily prepared using known synthetic methods, see for example, Lindstom et al., U.S. Patent No. 5,446,153 and the references cited therein.

In step (2) of Reaction Scheme I a 3-nitro-4-aminopyridine-2-sulfonate of Formula XI is reacted with dibenzylamine to provide a 2-dibenzylamino-3-nitropyridin-4-amine of Formula XII. The reaction is carried out by combining a compound of Formula XI, dibenzylamine, and a tertiary amine such as triethylamine in an inert solvent such as benzene, toluene or xylene and heating the resulting mixture.

In step (3) of Reaction Scheme I the nitro group of a 2-dibenzylamino-3-nitropyridin-4-amine of Formula XII is reduced to an amino group. The reduction is preferably carried out using NiB_2 which is generated in situ from sodium borohydride and nickel chloride hydrate in methanol. The reaction is preferably carried out at ambient temperature.

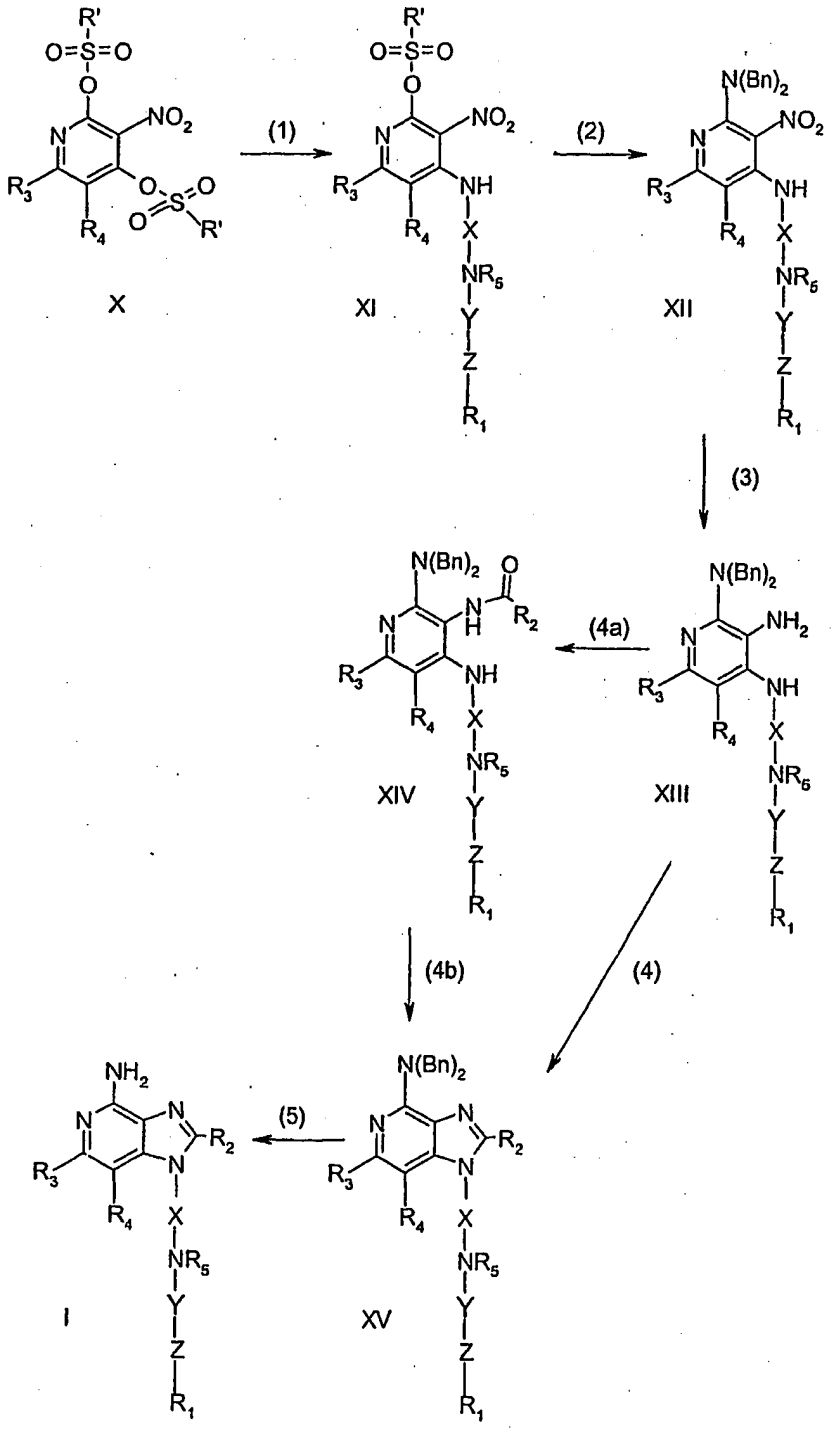
In step (4) of Reaction Scheme I a 2-dibenzylaminopyridine-3,4-diamine of Formula XIII is reacted with a carboxylic acid or an equivalent thereof to provide a 4-dibenzylamino-1*H*-imidazo[4,5-*c*]pyridine of Formula XV. Suitable equivalents to carboxylic acid include orthoesters and 1,1-dialkoxyalkyl alkanoates. The carboxylic acid or equivalent is selected such that it will provide the desired R_2 substituent in a compound of Formula XV. For example, triethyl orthoformate will provide a compound where R_2 is hydrogen and triethyl orthoacetate will provide a compound where R_2 is methyl. The reaction can be run in the absence of solvent or in an inert solvent such as toluene. The reaction is run with sufficient heating to drive off any alcohol or water formed as a byproduct of the reaction. Optionally a catlayst such as pyridine hydrochloride can be included.

Alternatively a compound of Formula XV can be prepared in two steps by (a) reacting a diamine of Formula XIII with an acyl halide of formula $R_2C(O)Cl$ or $R_2C(O)Br$ to provide a compound of Formula XIV and then (b) cyclizing. In step (4a) the acyl halide is added to a solution of the diamine in an inert solvent such as acetonitrile, pyridine or

dichloromethane. The reaction can be carried out at ambient temperature. In step (4b) the product of step (4a) is heated in an alcoholic solvent in the presence of a base. Preferably the product of step (4a) is refluxed in ethanol in the presence of an excess of triethylamine or heated with methanolic ammonia. Alternatively step (4b) can be carried out by heating the product of step (4a) in pyridine. If step (4a) was carried out in pyridine, step (4b) can be carried out by heating the reaction mixture after analysis indicates that step (4a) is complete.

In step (5) of Reaction Scheme I a 4-dibenzylamino-1*H*-imidazo[4,5-*c*]pyridine of Formula XV is hydrogenolyzed to provide the 4-amino-1*H*-imidazo[4,5-*c*]pyridine of Formula I. Preferably the compound of Formula XV is heated in formic acid in the presence of palladium hydroxide on carbon. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme I



Compounds of the invention can be prepared according to Reaction Scheme II where R_1, R_2, R_3, R_4, R_5 and X are as defined above, Bn is benzyl, BOC is *tert*-butoxycarbonyl and W is O or S.

In step (1) of Reaction Scheme II the amine protecting groups of a 1*H*-imidazo[4,5-*c*]pyridine of Formula XVI are removed to provide a 1*H*-imidazo[4,5-*c*]pyridine of Formula II. Preferably a solution of a compound of Formula XVI in a suitable solvent such as dichloromethane is treated with triflic acid at ambient temperature. Compounds of Formula XVI can be prepared using the synthetic method described in Reaction Scheme I. In step (1) a 2,4-disulfonate of Formula X is reacted with an amine of formula BOC-NR_5-X-NH_2. Steps 2-4 are then carried out as described above to provide a compound of Formula XVI which is a subgenus of Formula XV.

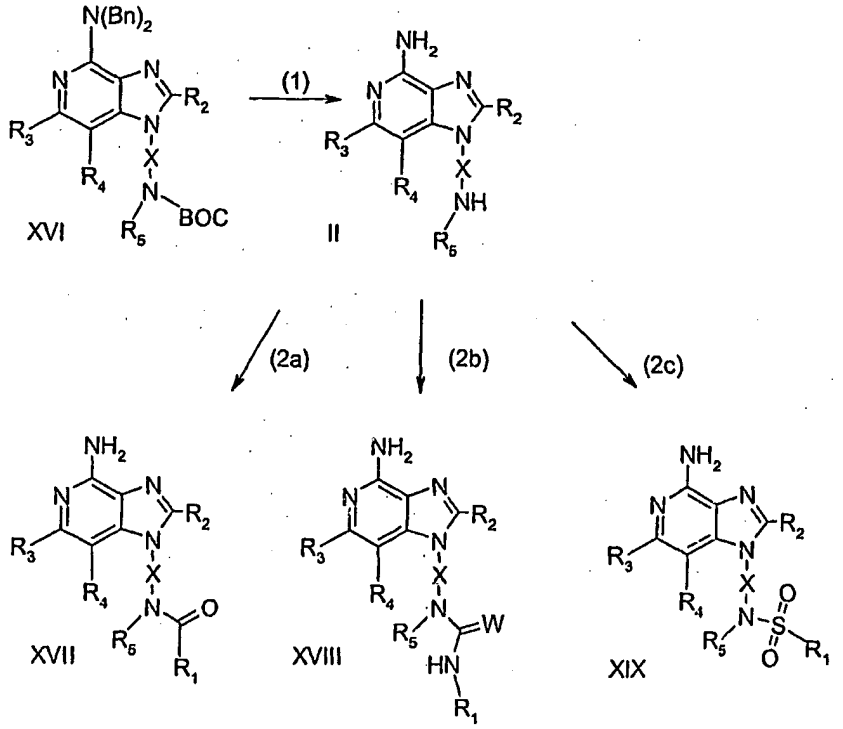
In step (2a) of Reaction Scheme II, a 1*H*-imidazo[4,5-*c*]pyridine of Formula II is reacted with an acid chloride of formula R_1-C(O)Cl or an acid anhydride of formula R_1-C(O)OC(O)-R_1 to provide a 1*H*-imidazo[4,5-*c*]pyridin-1-yl amide of Formula XVII which is a subgenus of Formula I. The reaction is preferably carried out by adding the acid chloride or acid anhydride to a solution of a compound of Formula II in a suitable solvent such as dichloromethane or acetonitrile in the presence of a base such as triethylamine. The reaction can be run at a reduced temperature (0°C) or at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (2b) of Reaction Scheme II, a 1*H*-imidazo[4,5-*c*]pyridine of Formula II is reacted with an isocyanate of formula R_1-N=C=O or with an isothiocyanate of formula R_1-N=C=S to provide a 1*H*-imidazo[4,5-*c*]pyridin-1-yl urea or thiourea of Formula XVIII which is a subgenus of Formula I. The reaction is preferably carried out by adding the isocyanate or isothiocyanate to a solution of a compound of Formula II in a suitable solvent such as dichloromethane at a reduced temperature (0°C). The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (2c) of Reaction Scheme II, a 1*H*-imidazo[4,5-*c*]pyridine of Formula II is reacted with a sulfonyl chloride of formula R_1-$S(O)_2$Cl or a sulfonic anhydride of formula R_1-$S(O)_2OS(O)_2$-R_1 to provide a 1*H*-imidazo[4,5-*c*]pyridin-1-yl sulfonamide of Formula XIX which is a subgenus of Formula I. The reaction is preferably carried out by adding the sulfonyl chloride or sulfonic anhydride to a solution of a compound of Formula II in a

suitable solvent such as dichloromethane in the presence of a base such as triethylamine. The reaction can be run at a reduced temperature (0°C) or at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

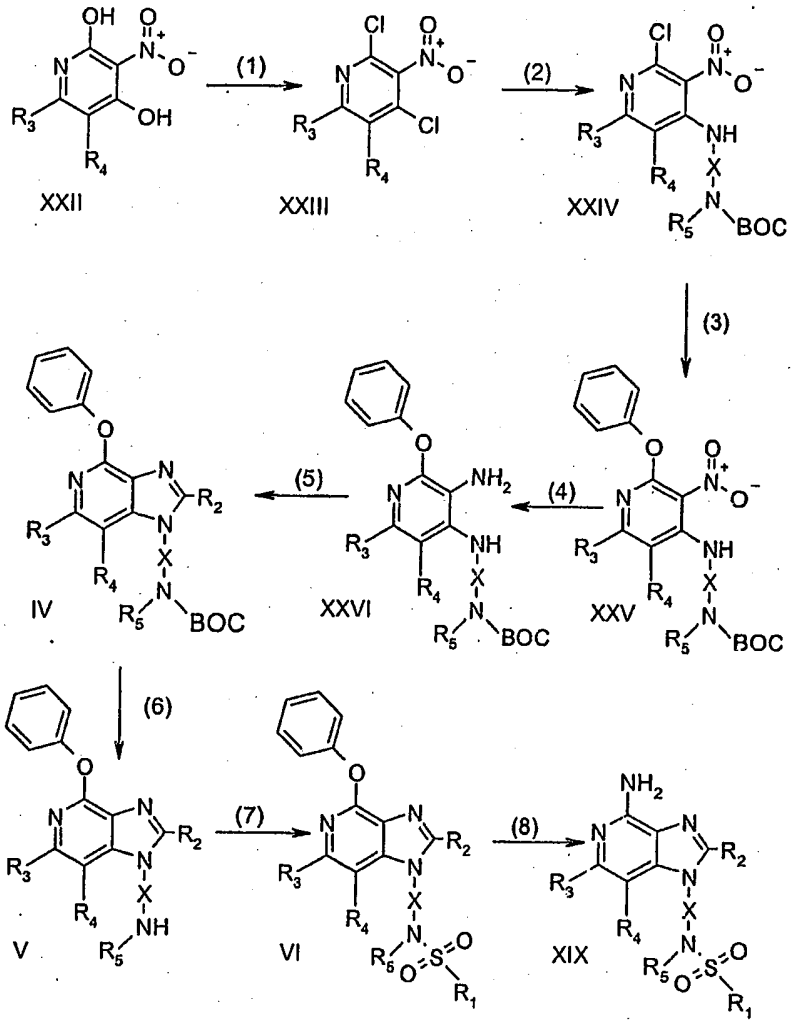
Reaction Scheme II



Compounds of the invention can be prepared according to Reaction Scheme III where R_1, R_2, R_3, R_4, R_5 and X, are as defined above.

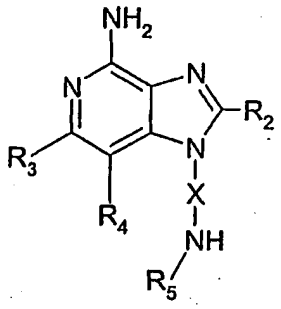
In step (1) of Reaction Scheme III a 1*H*-imidazo[4,5-*c*]pyridine of Formula II is reacted with a sulfamoyl chloride of formula R_1-N(R_5)S(O)$_2$Cl to provide a 1*H*-imidazo[4,5-*c*]pyridin-1-yl sulfamide of Formula XXI which is a subgenus of Formula I. Preferably the sulfamoyl chloride is added to a solution of the compound of Formula II in a suitable solvent such as 1,2-dichloroethane in the presence of a base such as triethylamine. The reaction can be run at an elevated temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme IV



The invention also provides novel compounds useful as intermediates in the synthesis of the compounds of Formula I. These intermediates have structural Formulas (II) - (VI) described in more detail below.

One class of intermediate compounds has Formula (II):



(II)

wherein: **X** is alkylene or alkenylene;

R_2 is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-alkyl-O-alkyl;

-alkyl-S-alkyl;

-alkyl-O-aryl;

-alkyl-S-aryl;

-alkyl-O- alkenyl;

-alkyl-S- alkenyl; and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

$-N(R_5)_2$;

$-CO-N(R_5)_2$;

$-CS-N(R_5)_2$;

$-SO_2-N(R_5)_2$;

$-NR_5-CO-C_{1-10}$ alkyl;

$-NR_5-CS-C_{1-10}$ alkyl;

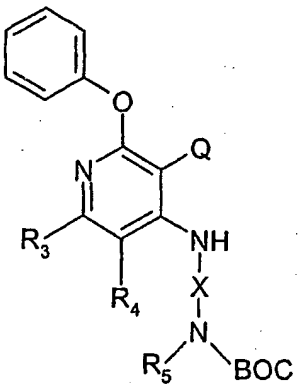
-NR_5- SO_2-C_{1-10} alkyl;
-CO-C_{1-10} alkyl;
-CO-O-C_{1-10} alkyl;
-N_3;
-aryl;
-heteroaryl;
-heterocyclyl;
-CO-aryl; and
-CO-heteroaryl;

R_3 and R_4 are independently selected from the group consisting of alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio; and

each R_5 is independently H or C_{1-10} alkyl;

or a pharmaceutically acceptable salt thereof.

Another class of intermediates has the Formula III:



(III)

wherein: Q is NO_2 or NH_2;

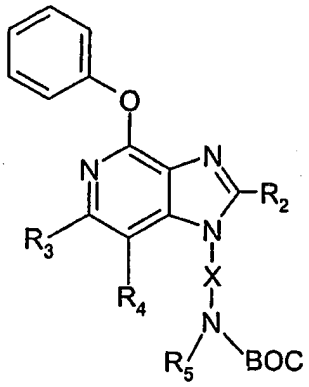
X is alkylene or alkenylene;

R_3 and R_4 are independently selected from the group consisting of alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio; and

each R_5 is independently H or C_{1-10} alkyl;

or a pharmaceutically acceptable salt thereof.

Another class of intermediates has the Formula (IV):



(IV)

wherein: **X** is alkylene or alkenylene;

$\mathbf{R_2}$ is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-alkyl-O-alkyl;

-alkyl-S-alkyl;

-alkyl-O-aryl;

-alkyl-S-aryl;

-alkyl-O- alkenyl;

-alkyl-S- alkenyl; and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

$-N(R_5)_2$;

$-CO-N(R_5)_2$;

$-CS-N(R_5)_2$;

$-SO_2-N(R_5)_2$;

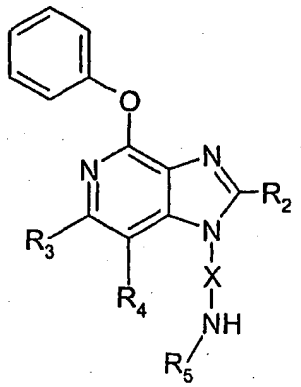
-NR_5-CO-C_{1-10} alkyl;
-NR_5-CS-C_{1-10} alkyl;
-NR_5- SO_2-C_{1-10} alkyl;
-CO-C_{1-10} alkyl;
-CO-O-C_{1-10} alkyl;
-N_3;
-aryl;
-heteroaryl;
-heterocyclyl;
-CO-aryl; and
-CO-heteroaryl;

R_3 and R_4 are independently selected from the group consisting of alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio; and

each R_5 is independently H or C_{1-10} alkyl;

or a pharmaceutically acceptable salt thereof.

Another class of intermediates has the Formula (V):



(V)

wherein: **X** is alkylene or alkenylene;

R_2 is selected from the group consisting of:

-hydrogen;
-alkyl;

-alkenyl;

-alkyl-O-alkyl;

-alkyl-S-alkyl;

-alkyl-O-aryl;

-alkyl-S-aryl;

-alkyl-O- alkenyl;

-alkyl-S- alkenyl; and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

-$N(R_5)_2$;

-$CO\text{-}N(R_5)_2$;

-$CS\text{-}N(R_5)_2$;

-$SO_2\text{-}N(R_5)_2$;

-$NR_5\text{-}CO\text{-}C_{1\text{-}10}$ alkyl;

-$NR_5\text{-}CS\text{-}C_{1\text{-}10}$ alkyl;

-$NR_5\text{-}SO_2\text{-}C_{1\text{-}10}$ alkyl;

-$CO\text{-}C_{1\text{-}10}$ alkyl;

-$CO\text{-}O\text{-}C_{1\text{-}10}$ alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

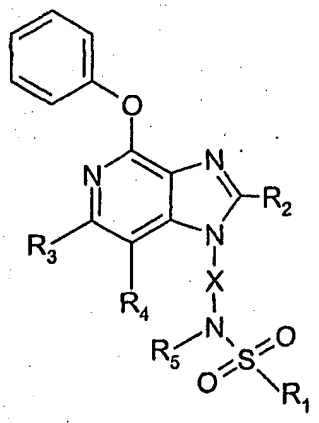
-CO-heteroaryl;

R_3 and R_4 are independently selected from the group consisting of alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio; and

each R_5 is independently H or $C_{1\text{-}10}$ alkyl;

or a pharmaceutically acceptable salt thereof.

Another class of intermediates has the Formula (VI):



(VI)

wherein: **X** is alkylene or alkenylene;

R_1 is aryl, heteroaryl, heterocyclyl, C_{1-20} alkyl or C_{2-20} alkenyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of:

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-substituted cycloalkyl;

-O-alkyl;

-O-$(alkyl)_{0-1}$-aryl;

-O-$(alkyl)_{0-1}$-heteroaryl;

-O-$(alkyl)_{0-1}$-heterocyclyl;

-COOH;

-CO-O-alkyl;

-CO-alkyl;

-$S(O)_{0-2}$ -alkyl;

-$S(O)_{0-2}$ –$(alkyl)_{0-1}$-aryl;

-$S(O)_{0-2}$–$(alkyl)_{0-1}$-heteroaryl;

-$S(O)_{0-2}$–$(alkyl)_{0-1}$-heterocyclyl;

-$(alkyl)_{0-1}$-$N(R_5)_2$;

-$(alkyl)_{0-1}$-NR_5-CO-O-alkyl;

-$(alkyl)_{0-1}$-NR_5-CO-alkyl;

-$(alkyl)_{0-1}$-NR_5-CO-aryl;

-$(alkyl)_{0-1}$-NR_5-CO-heteroaryl;

-N_3;

-halogen;

-haloalkyl;

-haloalkoxy;

-CO-haloalkyl;

-CO-haloalkoxy;

-NO_2;

-CN;

-OH;

-SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R_2 is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-alkyl-O-alkyl;

-alkyl-S-alkyl;

-alkyl-O-aryl;

-alkyl-S-aryl;

-alkyl-O- alkenyl;

-alkyl-S- alkenyl; and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

-$N(R_5)_2$;

-CO-N(R_5)$_2$;
-CS-N(R_5)$_2$;
-SO_2-N(R_5)$_2$;
-NR_5-CO-C_{1-10} alkyl;
-NR_5-CS-C_{1-10} alkyl;
-NR_5- SO_2-C_{1-10} alkyl;
-CO-C_{1-10} alkyl;
-CO-O-C_{1-10} alkyl;
-N_3;
-aryl;
-heteroaryl;
-heterocyclyl;
-CO-aryl; and
-CO-heteroaryl;

R_3 and R_4 are independently selected from the group consisting of alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio; and

each R_5 is independently H or C_{1-10} alkyl;

or a pharmaceutically acceptable salt thereof.

As used herein, the terms "alkyl", "alkenyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms. Preferred groups have a total of up to 10 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, and adamantyl.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of groups that include the prefix "halo-". Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl. The

term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring hetero atom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, and so on.

"Heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring hetero atom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, isothiazolidinyl, and imidazolidinyl.

The aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, alkylthio, haloalkyl, haloalkoxy, haloalkylthio, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylthio, arylalkoxy, arylalkylthio, heteroaryl, heteroaryloxy, heteroarylthio, heteroarylalkoxy, heteroarylalkylthio, amino, alkylamino, dialkylamino, heterocyclyl, heterocycloalkyl, alkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, haloalkylcarbonyl, haloalkoxycarbonyl, alkylthiocarbonyl, arylcarbonyl, heteroarylcarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, arylthiocarbonyl, heteroarylthiocarbonyl, alkanoyloxy, alkanoylthio, alkanoylamino, arylcaronyloxy, arylcarbonythio, alkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryldiazinyl, alkylsulfonylamino, arylsulfonylamino, arylalkylsulfonylamino, alkylcarbonylamino, alkenylcarbonylamino, arylcarbonylamino, arylalkylcarbonylamino, heteroarylcarbonylamino, heteroarylalkycarbonylamino, alkylsulfonylamino, alkenylsulfonylamino, arylsulfonylamino, arylalkylsulfonylamino, heteroarylsulfonylamino, heteroarylalkylsulfonylamino, alkylaminocarbonylamino, alkenylaminocarbonylamino, arylaminocarbonylamino, arylalkylaminocarbonylamino, heteroarylaminocarbonylamino, heteroarylalkylaminocarbonylamino and, in the case of heterocyclyl, oxo. If other groups are described as being "substituted" or "optionally substituted", then those groups can also be substituted by one or more of the above enumerated substituents.

Certain substituents are generally preferred. For example, preferred Y groups are

– CO – and –SO_2-; Z is preferably a bond or – NR_5 -; and R_1 is preferably C_{1-4} alkyl, aryl, or substituted aryl. Preferred R_2 groups include alkyl groups having 1 to 4 carbon atoms (i.e., methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and tert-butyl), methoxyethyl, ethoxymethyl, and cyclopropylmethyl. R_3 and R_4 are preferably methyl. One or more of these preferred substitutents, if present, can be present in the compounds of the invention in any combination.

The invention is inclusive of the compounds described herein in any of their pharmaceutically acceptable forms, including isomers such as diastereomers and enantiomers, salts, solvates, polymorphs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers.

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound of the invention as described above in combination with a pharmaceutically acceptable carrier.

The term "a therapeutically effective amount" means an amount of the compound sufficient to induce a therapeutic effect, such as cytokine induction, antitumor activity, and/or antiviral activity. Although the exact amount of active compound used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg, of the compound to the subject. Any of the conventional dosage forms may be used, such as tablets, lozenges, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like.

The compounds of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds of the invention may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, etc.

The compounds of the invention have been shown to induce the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds are useful as immune response modifiers that can modulate the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds according to the invention generally include interferon-α (IFN-α) and/or tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds of the invention include IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds useful in the treatment of viral diseases and tumors. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or composition of the invention to the animal.

Certain compounds of the invention have been found to preferentially induce the expression of IFN-α in a population of hematopoietic cells such as PBMCs (peripheral blood mononuclear cells) containing pDC2 cells (precursor dendritic cell-type 2) without concomitant production of significant levels of inflammatory cytokines.

In addition to the ability to induce the production of cytokines, the compounds of the invention affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds may also activate macrophages, which in turn stimulates secretion of nitric oxide and the production of additional cytokines. Further, the compounds may cause proliferation and differentiation of B-lymphocytes.

Compounds of the invention also have an effect on the acquired immune response. For example, although there is not believed to be any direct effect on T cells or direct induction of T cell cytokines, the production of the T helper type 1 (Th1) cytokine IFN-γ is induced indirectly and the production of the T helper type 2 (Th2) cytokines IL-4, IL-5 and IL-13 are inhibited upon administration of the compounds. This activity means that the compounds are useful in the treatment of diseases where upregulation of the Th1 response and/or downregulation of the Th2 response is desired. In view of the ability of compounds of the invention to inhibit the Th2 immune response, the compounds are

expected to be useful in the treatment of atopic diseases, e.g., atopic dermatitis, asthma, allergy, allergic rhinitis; systemic lupus erythematosis; as a vaccine adjuvant for cell mediated immunity; and possibly as a treatment for recurrent fungal diseases and chlamydia.

The immune response modifying effects of the compounds make them useful in the treatment of a wide variety of conditions. Because of their ability to induce the production of cytokines such as IFN-α and/or TNF-α, the compounds are particularly useful in the treatment of viral diseases and tumors. This immunomodulating activity suggests that compounds of the invention are useful in treating diseases such as, but not limited to, viral diseases including genital warts; common warts; plantar warts; Hepatitis B; Hepatitis C; Herpes Simplex Virus Type I and Type II; molluscum contagiosum; variola, particularly variola major; HIV; CMV; VZV; rhinovirus; adenovirus; coronavirus; influenza; and para-influenza; intraepithelial neoplasias such as cervical intraepithelial neoplasia; human papillomavirus (HPV) and associated neoplasias; fungal diseases, e.g. candida, aspergillus, and cryptococcal meningitis; neoplastic diseases, e.g., basal cell carcinoma, hairy cell leukemia, Kaposi's sarcoma, renal cell carcinoma, squamous cell carcinoma, myelogenous leukemia, multiple myeloma, melanoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, and other cancers; parasitic diseases, e.g. pneumocystis carnii, cryptosporidiosis, histoplasmosis, toxoplasmosis, trypanosome infection, and leishmaniasis; and bacterial infections, e.g., tuberculosis, and mycobacterium avium. Additional diseases or conditions that can be treated using the compounds of the invention include actinic keratosis; eczema; eosinophilia; essential thrombocythaemia; leprosy; multiple sclerosis; Ommen's syndrome; discoid lupus; Bowen's disease; Bowenoid papulosis; alopecia areata; the inhibition of Keloid formation after surgery and other types of post-surgical scars. In addition, these compounds could enhance or stimulate the healing of wounds, including chronic wounds. The compounds may be useful for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

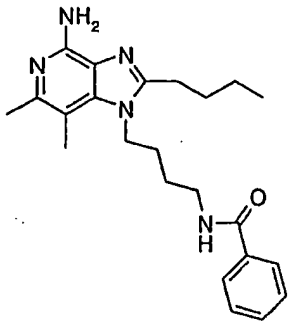
An amount of a compound effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α,

TNF-α, IL-1, IL-6, IL-10 and IL-12 that is increased over the background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 µg/kg to about 5 mg/kg. The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 µg/kg to about 5 mg/kg. An amount of a compound effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 µg/kg to about 5 mg/kg.

The invention is further described by the following examples, which are provided for illustration only and are not intended to be limiting in any way.

Example 1

N-[4-(4-Amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]benzamide



Part A

Triethylamine (16.8 mL, 123.8 mmol) was added to a suspension of 4-hydroxy-5,6-dimethyl-3-nitro-2(1H)-pyridone (7.6 g, 41.2 mmol) in dichloromethane (200 mL).

The resulting mixture was cooled in an ice bath. Triflic anhydride (13.7 mL, 82.5 mmol) was added and the reaction mixture was stirred for 30 minutes. Mono-*tert*-butoxycarbonyl-1,4-butyldiamine (7.6 g, 41.2 mmol) was added in a single portion and the reaction mixture was allowed to warm to ambient temperature. After 1 hour the reaction mixture was washed with aqueous 1% sodium carbonate (2 X 100 mL), dried over magnesium sulfate and then concentrated under reduced pressure to provide crude product. This material was dissolved in dichloromethane and loaded onto a layer of silica gel. The silica gel was eluted first with dichloromethane to remove some impurities and then with 2-5% ethyl acetate in dichloromethane to recover the desired product. The fractions containing product were combined and then concentrated under reduced pressure to provide 12 g of 4-({4-[(*tert*-butoxycarbonyl)amino]butyl}amino)-5,6-dimethyl-3-nitropyridin-2-yl trifluoromethanesulfonate as a light yellow oil.

Part B

The material from Part A was combined with triethylamine (2.5 g, 24.7 mmol), dibenzylamine (4.8 g, 24.7 mmol), and toluene (150 mL) and then heated at reflux for 4 hours. The reaction mixture was washed with aqueous 1% sodium carbonate and then concentrated under reduced pressure to provide crude product. This material was dissolved in dichloromethane and loaded onto silica gel. The silica gel was eluted with 2-20% ethyl acetate in dichloromethane. The fractions containing product were combined and then concentrated under reduced pressure to provide ~13 g of *tert*-butyl 4-{[2-(dibenzylamino)-5,6-dimethyl-3-nitropyridin-4-yl]amino}butylcarbamate.

Part C

Sodium borohydride (1.4 g, 36 mmol) was slowly added to a solution of nickel chloride hydrate (2.9 g, 12.3 mmol) in methanol and the resulting mixture was stirred for 30 minutes. A solution of the material from Part B in methanol was added in a single portion. Sodium borohydride was slowly added until the foaming was colorless. The reaction mixture was filtered. The filtrate was concentrated under reduced pressure. The resulting residue was combined with dichloromethane and the mixture was filtered to remove salts. The filtrate was concentrated under reduced pressure to provide ~12 g of *tert*-butyl 4-{[3-amino-2-(dibenzylamino)-5,6-dimethylpyridin-4-yl]amino}butylcarbamate.

Part D

Valeryl chloride (3 mL, 24.7 mmol) was added to a solution of the material from Part C in acetonitrile (200 mL). The reaction mixture was stirred at ambient temperature. The reaction mixture was concentrated under reduced pressure. The residue was combined with ethanol and triethylamine (5 g, 49 mmol.). The reaction mixture was heated at reflux overnight and then concentrated under reduced pressure. The resulting residue was partitioned between dichloromethane and water. The dichloromethane layer was separated and then loaded onto a silica gel column. The column was eluted with 9:90:1 ethyl acetate:dichloromethane: methanol. The fractions containing product were combined and then concentrated under reduced pressure to provide 6.5 g of *tert*-butyl 4-[2-butyl-4-(dibenzylamino)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butylcarbamate as an oil.

Part E

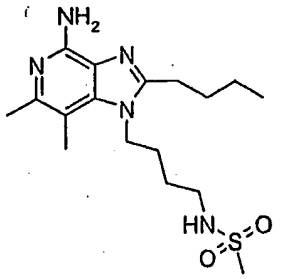
Triflic acid (16g, 107 mmol) was added to a solution of the material from Part D (6.5g, 11.4 mmol) in dichloromethane (250 mL). The resulting mixture was stirred overnight. Ammonium hydroxide (50 mL) and water (100 mL) were added and the resulting mixture was stirred for 30 minutes. The layers were separated and the aqueous fraction was extracted with dichloromethane (100 mL). The organic fractions were combined, washed with 1% aqueous sodium carbonate, washed with brine and concentrated under reduced pressure. The residue was combined with methanol (30 mL), stirred for 30 minutes and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was combined with 1% aqueous sodium carbonate and stirred. The mixture was extracted with hexane to remove organic impurities. The aqueous layer contained an insoluble oil that was extracted with dichloromethane. The organic layer was combined with magnesium sulfate, stirred for 5 minutes and filtered. The filtrate was concentrated under reduced pressure to provide a solid which was recrystallized from toluene to provide 1g of 1-(4-aminobutyl)-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine.

Part F

Triethylamine (0.07 mL, 0.5 mmol) was added to a solution of 1-(4-aminobutyl)-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (150 mg, 0.5 mmol) in dichloromethane (150 mL). The reaction mixture was cooled in an ice bath. Benzoyl chloride (0.07 mL, 0.5 mmol) was added and the reaction mixture was removed from the ice bath. The reaction mixture was washed twice with water and then concentrated under reduced pressure. The resulting residue was purified by flash chromatography eluting with 10% methanol in dichloromethane to provide an oily brown material. This material was dissolved in a minimum amount of isopropanol and then ethanesulfonic acid (55 mg, 0.5 mmol) was added with stirring. The reaction mixture was stirred at ambient temperature for ~1 hour and then heated briefly in a sand bath until it became homogeneous. The solution was allowed to cool to ambient temperature and then was chilled in an ice bath. The resulting precipitate was isolated by filtration to provide 111 mg of *N*-[4-(4-amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]benzamide as a crystalline solid, m.p. 127.8-128.8°C.
Analysis: Calculated for $C_{23}H_{31}N_5O$: %C, 70.20; %H, 7.94; %N, 17.80; Found: %C, 69.82; %H, 7.70; %N, 17.68.

Example 2

N-[4-(4-Amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]methanesulfonamide



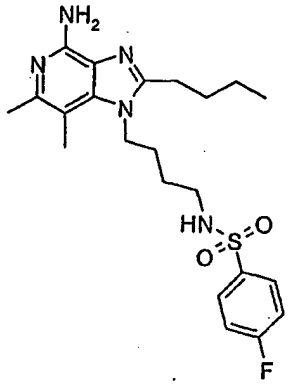
Triethylamine (0.07 mL, 0.5 mmol) was added to a solution of 1-(4-aminobutyl)-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (150 mg, 0.5 mmol) in dichloromethane (160 mL). The reaction mixture was cooled in an ice bath.

Methanesulfonic anhydride (90 mg, 0.5 mmol) was added and the reaction mixture was removed from the ice bath. The reaction mixture was stirred for 35 minutes. The reaction mixture was washed three times with water, concentrated under reduced pressure, and triturated with a minimum volume of methyl acetate. The resulting crystalline solid was isolated by filtration and then dried in an Abderhalden drying apparatus to provide 94 mg of *N*-[4-(4-amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]methanesulfonamide, m.p. 130-130.5°C

Analysis: Calculated for $C_{17}H_{29}N_5O_2S$: %C, 55.56; %H, 7.95; %N, 19.06; Found: %C, 55.37; %H, 7.89; %N, 18.03.

Example 3

N-[4-(4-Amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-4-fluorobenzenesulfonamide Hydrate

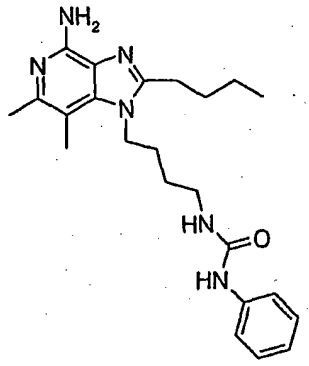


Triethylamine (0.07 mL, 0.5 mmol) was added to a solution of 1-(4-aminobutyl)-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (150 mg, 0.5 mmol) in dichloromethane (150 mL). The reaction mixture was cooled in an ice bath. 4-Fluorobenzenesulfonyl chloride (113 mg, 0.5 mmol) was added and the reaction mixture was removed from the ice bath. The reaction mixture was stirred at ambient temperature for 48 hours. The reaction mixture was washed with water (2 X 150 mL) and then concentrated under reduced pressure. The resulting residue was recrystallized from methyl acetate and then dried in an Abderhalden drying apparatus to provide 50 mg of *N*-

[4-(4-amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-4-fluorobenzenesulfonamide hydrate as a white crystalline solid, m.p. 133.1-133.7°C. Analysis: Calculated for $C_{22}H_{30}FN_5O_2S \cdot H_2O$: %C, 56.75; %H, 6.93; %N, 15.04; Found: %C, 56.99; %H, 6.58; %N, 15.24.

Example 4

N-[4-(4-Amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-*N'*-phenylurea

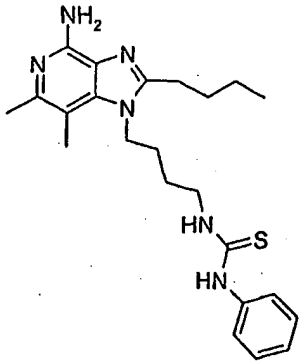


Phenylisocyanate (0.056 mL, 0.5 mmol) was added to a chilled solution of of 1-(4-aminobutyl)-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (150 mg, 0.5 mmol) in dichloromethane (150 mL). The ice bath was removed. A white precipitate formed after 5 minutes. The reaction mixture was allowed to stir for 30 minutes and then it was concentrated under reduced pressure to provide an off-white crystalline solid. This material was isolated by filtration using a small amount of diethyl ether to transfer the material to the filter and then dried in an Abderhalden drying apparatus to provide 185 mg of *N*-[4-(4-amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-*N'*-phenylurea, m.p. 195.8-196.8°C.

Analysis: Calculated for $C_{23}H_{32}N_6O$: %C, 67.62; %H, 7.89; %N, 20.57; Found: %C, 66.84; %H, 7.71; %N, 20.54.

Example 5

N-[4-(4-Amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-*N'*-phenylthiourea Hydrate

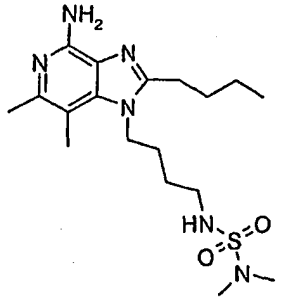


Using the method of Example 4, 1-(4-aminobutyl)-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (100 mg, 0.35 mmol) was reacted with phenylisothiocyanate (0.041 mL, 0.35 mmol) to provide 97 mg of *N*-[4-(4-amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-*N'*-phenylthiourea hydrate as a white crystalline solid, m.p. 160.0-160.8°C.

Analysis: Calculated for $C_{23}H_{32}N_6S \cdot H_2O$: %C, 62.41; %H, 7.74; %N, 18.99; Found: %C, 62.39; %H, 7.47; %N, 18.52.

Example 6

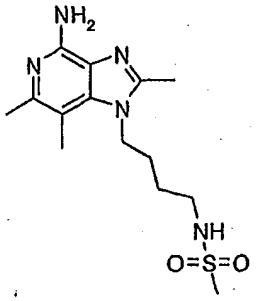
N'-[4-(4-Amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-*N,N*-dimethylsulfamide



Triethylamine (0.031 mL, 0.23 mmol) was added to a solution of 1-(4-aminobutyl)-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (67 mg, 0.23 mmol) in dichloromethane (45 mL). The reaction mixture was cooled in an ice bath. Dimethylsulfamoyl chloride (0.025 mL, 0.23 mmol) was added. The reaction mixture was removed from the ice bath. The reaction mixture was allowed to stir at ambient temperature for ~113 hours. Analysis by HPLC indicated that the reaction was not complete. The dichloromethane was removed under reduced pressure. 1,2-Dichloroethane (50 mL) was added and the reaction mixture was heated to 60°C. After 3 hours, more dimethylsulfamoyl chloride (2.5 µL) was added and heating was continued. After 22 hours the reaction temperature was raised to reflux and the reaction mixture was refluxed for 100 hours. The reaction mixture was extracted twice with water. The aqueous fractions were combined and concentrated under reduced pressure. The resulting residue was recrystallized from methyl acetate to provide 10 mg of *N'*-[4-(4-amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-*N,N*-dimethylsulfamide as an off-white crystalline solid, m.p. 129.5-131°C. M/Z = 397.1 $(M + H)^+$.

Example 7

N-[4-(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]methanesulfonamide



Part A

A mixture of 5,6-dimethyl-3-nitropyridine-2,4-diol (60.0 g, 326 mmol) and phosphorus oxychloride (600 mL) was heated at reflux for 2 hrs. The reaction mixture was concentrated under reduced pressure. The resulting residue was combined with ethyl

acetate (300 mL) and then filtered. The filtrate was washed with aqueous sodium bicarbonate solution. The layers were separated and aqueous layer was extracted twice with ethyl acetate. The organic layers were combined, dried with magnesium sulfate and then concentrated under reduced pressure to provide a brown solid. This material was purified by chromatography (silica gel eluting with 60/40 ethyl acetate/hexanes) to provide 55 g of 2,4-dichloro-5,6-dimethyl-3-nitropyridine.

Part B

Tert-butyl 4-aminobutylcarbamate (60 g, 339 mmol) was slowly added to a mixture of 2,4-dichloro-5,6-dimethyl-3-nitropyridine (50 g, 226 mmol), anhydrous N,N-dimethylformamide (500 mL) and triethylamine (50 mL, 339 mmol). The reaction mixture was allowed to stir overnight and then it was concentrated under reduced pressure to provide an oil. The oil was dissolved in ethyl acetate and then washed with water. The organic layer was dried over magnesium sulfate and then concentrated under reduced pressure to provide a dark oil. This material was purified by column chromatography (silica gel eluting with 40/60 ethyl acetate/hexanes) to provide 64.5 g of *tert*-butyl 4-(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)butylcarbamate as a bright orange oil which solidified on standing.

Part C

A solution of phenol (18.50 g, 196 mmol) in diglyme (50 mL) was slowly added dropwise to a chilled (0°C) suspension of sodium hydride (8.28 g of 60% in mineral oil, 207 mmol) in diglyme (50 mL). After 1 hr gas evolution ceased. A solution of *tert*-butyl 4-(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)butylcarbamate (68.95 g, 185 mmol) in diglyme (200 mL) was slowly added dropwise to the reaction mixture. After the addition was complete the reaction mixture was heated at reflux for 4 hrs. The reaction mixture was concentrated under reduced pressure to provide a black oil. The oil was dissolved in ethyl acetate and then extracted with 1N sodium hydroxide to remove excess phenol. The organic layer was dried over magnesium sulfate and then concentrated under reduced pressure. The residue was purified by chromatography (silica gel eluting with 30/70 ethyl acetate/hexanes) to provide 40.67 g of *tert*-butyl 4-[(2,3-dimethyl-5-nitro-6-phenoxypyridin-4-yl)amino]butylcarbamate as an orange oil.

Part D

Tert-butyl 4-[(2,3-dimethyl-5-nitro-6-phenoxypyridin-4-yl)amino]butylcarbamate (9.17 g, 21.3 mmol), toluene (50 mL), isopropanol (5 mL) and 5% platinum on carbon (7.0 g) were combined and maintained under hydrogen pressure (50 psi, 3.5 Kg/cm^2) overnight on a Parr apparatus. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The resulting brown oil was dried under high vacuum to provide 7.47 g of *tert*-butyl 4-[(3-amino-5,6-dimethyl-2-phenoxypyridin-4-yl)amino]butylcarbamate.

Part E

A mixture of the material from Part D, triethyl orthoacetate (3.59 mL, 19.58 mmol), anhydrous toluene (75 mL) and pyridine hydrochloride (0.75 g) was heated at reflux for 1 hour and then concentrated under reduced pressure to provide a brown oil. The oil was dissolved in ethyl acetate and then washed with water (X2), washed with brine, dried over magnesium sulfate and then concentrated under reduced pressure to provide 6.74 g of *tert*-butyl 4-(2,6,7-trimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butylcarbamate as a brown oil.

Part F

A solution of *tert*-butyl 4-(2,6,7-trimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butylcarbamate (6.70 g, 15.8 mmol) in dichloromethane (50 mL) was slowly added to a chilled (0°C) mixture of trifluoroacetic acid (60 mL) and dichloromethane (100 mL). The reaction mixture was allowed to warm to ambient temperature and then left overnight. The reaction mixture was concentrated under reduced pressure to provide a brown oil. The oil was dissolved in dichloromethane and the solution was made basic (pH 14) with 5% aqueous sodium hydroxide. The layers were separated and the aqueous layer was extracted with dichloromethane. The organic layers were combined, dried over magnesium sulfate and then concentrated under reduced pressure to provide 4.50 g of 4-(2,6,7-trimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butylamine as a brown oil.

Part G

A mixture of the material from Part F, triethylamine (2.0 mL, 14.6 mmol) and anhydrous acetonitrile (450 mL) was heated until a homogeneous solution was obtained. Methanesulfonic anhydride (2.54 g, 14.6 mmol) was slowly added to the reaction mixture. The reaction was judged to be complete in 10 minutes. The reaction mixture was

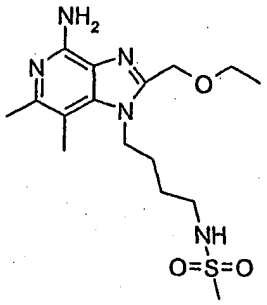
concentrated under reduced pressure to provide a brown oil. The oil was dissolved in dichloromethane and was washed with 5% aqueous sodium hydroxide. The aqueous layer was separated and then extracted with dichloromethane. The organic layers were combined, dried over magnesium sulfate and then concentrated under reduced pressure to provide a brown solid. This material was purified by column chromatography (silica gel eluting with 95/5 dichloromethane/methanol) to provide 4.49 g of *N*-[4-(2,6,7-trimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]methanesulfonamide as a light brown solid.

Part H

N-[4-(2,6,7-trimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]methanesulfonamide (4.20 g, 10.4 mmol) and ammonium acetate (42 g) were combined and then heated in a sealed tube at 150°C for 36 hrs. The reaction mixture was allowed to cool and then it was dissolved in chloroform. The solution was extracted with 10 % aqueous sodium hydroxide solution. The aqueous layer was separated and then extracted multiple times with chloroform. The organic layers were combined, dried over magnesium sulfate and then concentrated under reduced pressure to provide a yellow oil. The oil was dissolved in methanol and combined with 1M hydrochloric acid in diethyl ether (10.4 mL). The resulting white precipitate was isolated by filtration and dried. The solid was dissolved in water and the solution was adjusted to pH 10 with solid sodium carbonate. The resulting white precipitate was isolated by filtration, washed with diethyl ether and then dried in a vacuum oven at 80°C to provide 2.00 g of *N*-[4-(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]methanesulfonamide, m.p. 228-230°C. Analysis: Calculated for $C_{14}H_{23}N_5O_2S$: %C, 51.67; %H, 7.12; %N, 21.52; Found: %C, 51.48; %H, 6.95; %N, 21.51.

Example 8

N-{4-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}methanesulfonamide



Part A

Triethylamine (3.3 mL, 23.7 mmol) was added to a chilled (0°C) mixture of *tert*-butyl 4-[(3-amino-5,6-dimethyl-2-phenoxypyridin-4-yl)amino]butylcarbamate (8.60 g, 21.5 mmol) and anhydrous dichloromethane (200 mL). Ethoxyacetyl chloride (2.76 g, 22.5 mmol) was added. After one hour the reaction mixture was allowed to warm to ambient temperatureand stirred for 2 hours. The reaction mixture was concentrated under reduced pressure to provide *tert*-butyl 4-({3-[(ethoxyacetyl)amino]-5,6-dimethyl-2-phenoxypyridin-4-yl}amino)butylcarbamate as a brown oil. The oil was combined with pyridine (130 mL) and heated at reflux overnight. The reaction mixture was concentrated under reduced pressure to provide a brown oil. The oil was dissolved in dichloromethane and was washed with water. The organic layer was dried over magnesium sulfate and then concentrated under reduced pressure. The residue was dissolved in diethyl ether and then concentrated under reduced pressure to provide 8.21 g of *tert*-butyl 4-[2-(ethoxymethyl)-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butylcarbamate.

Part B

Using the method of Part F of Example 7, the material from Part A was hydrolyzed to provide 5.76 g of 4-[2-(ethoxymethyl)-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butan-1-amine as a brown oil.

Part C

Using the method of Part G of Example 7, 4-[2-(ethoxymethyl)-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butan-1-amine (5.52 g, 15.0 mmol) was reacted

with methanesulfonic anhydride (2.74 g, 15.7 mmol) to provide 6.26 g of *N*-{4-[2-(ethoxymethyl)-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}methanesulfonamide as a brown solid.

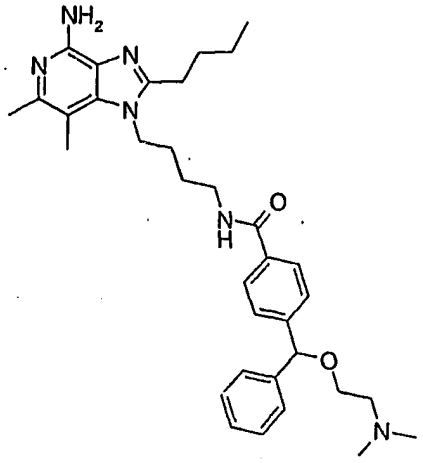
Part D

Using the general method of Part H of Example 7, *N*-{4-[2-(ethoxymethyl)-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}methanesulfonamide (5.86 g, 13.1 mmol) was aminated to provide 1.58 g of *N*-{4-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}methanesulfonamide as a white solid, m.p. 165-167°C.

Analysis: Calculated for $C_{16}H_{27}N_5O_3S$: %C, 52.01; %H, 7.37; %N, 18.95; Found: %C, 51.83; %H, 7.39; %N, 18.88.

Example 9

N-[4-(4-Amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-4-[[2-(dimethylamino)ethoxy](phenyl)methyl]benzamide



Part A

Under a nitrogen atmosphere, 4-(2-butyl-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butan-1-amine (122 mg, 0.33 mmol) was dissolved in dichloromethane and triethylamine (0.093 mL, 0.67 mmol). The solution was cooled in an ice-water bath and 4-[[2-(dimethylamino)ethoxy](phenyl)methyl]benzoyl chloride (106 mg, 0.33 mmol) was

dissolved/slurried in dichloromethane and added dropwise. The ice bath was removed and the reaction was stirred for an additional 16 hours. The reaction was quenched with 10% aqueous sodium carbonate. The phases were separated and the aqueous fraction was extracted with dichloromethane. The organic fractions were combined, washed with water followed by brine, dried (Na_2SO_4), decanted and evaporated to yield a yellow oil. Purification by flash column chromatography (silica gel, 92:8 dichloromethane/methanol gradient to 95:5 dichloromethane/methanol) provided 101 mg of N-[4-(2-butyl-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-4-[[2-(dimethylamino)ethoxy](phenyl)methyl]benzamide as a pale yellow solid. The product was determined to be 97+% pure by HPLC.

MS(CI): 648 (M+H).

Part B

N-[4-(2-Butyl-6,7-dimethyl-4-phenoxy-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-4-[[2-(dimethylamino)ethoxy](phenyl)methyl]benzamide (101 mg, 0.16 mmol) and ammonium acetate (1.1 g) were placed into a pressure tube along with a stir bar. The tube was sealed and heated at 150°C for 16 hours. The reaction was cooled to room temperature and diluted with water. The resulting cloudy aqueous mixture was made basic with 10% aqueous sodium hydroxide and extracted with chloroform (3 x 25mL). The combined organic fractions were washed with water followed by brine, dried (Na_2SO_4), decanted and evaporated to provide a yellow oil. Purification by flash column chromatography (silica gel, 95:5 dichloromethane/methanol gradient to 9:1 dichloromethane/methanol and finally 94:5:1 dichloromethane/methanol/triethylamine) provided 14 mg of N-[4-(4-amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-4-[[2-(dimethylamino)ethoxy](phenyl)methyl]benzamide as a yellow oil.

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.41 (t, J = 5.5 Hz, 1H), 7.76.(d, J = 8.3 Hz, 2H); 7.43 (d, J = 8.3, 2H), 7.37-7.31 (m, 4H), 7.26-7.22 (m, 1H), 5.84 (bs, 2H), 5.52 (s, 1H), 4.22 (t, J = 7.7 Hz, 2H), 3.49 (t, J = 5.8 Hz, 2H), 3.29 (dd, J = 6.4, 12.4 Hz, 2H), 2.76 (t, J = 7.7 Hz, 2H), 2.58 (t, J = 5.7 Hz, 2H), 2.32 (s, 3H), 2.27 (s, 3H), 2.22 (s, 6H), 1.73-1.65 (m, 4H), 1.61-1.55 (m, 2H), 1.35 (sextet, J = 7.4 Hz, 2H), 0.86 (t, J = 7.4 Hz, 3H);

^{13}C-NMR (125 MHz, DMSO-d_6) δ 165.9, 153.0, 148.1, 145.4, 142.0, 138.6, 133.5, 128.23, 127.4, 127.3, 127.1, 126.4, 126.1, 124.5, 103.0, 82.0, 66.3, 58.0, 45.2, 43.6, 38.4, 29.3, 28.8, 26.1, 26.0, 21.7, 21.0, 13.6, 12.2.

HRMS (CI) m/e 571.3763 (M+H), (571.3761 calcd for $C_{34}H_{47}N_6O_2$, M+H).

CYTOKINE INDUCTION IN HUMAN CELLS

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon (α) and tumor necrosis factor (α) (IFN and TNF, respectively) secreted into culture media as described by Testerman et. al. In "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", Journal of Leukocyte Biology, **58**, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBMCs) are separated from whole blood by density gradient centrifugation using Histopaque®-1077. The PBMCs are washed twice with Hank's Balanced Salts Solution and then are suspended at 3-4 x 10^6 cells/mL in RPMI complete. The PBMC suspension is added to 48 well flat bottom sterile tissue culture plates (Costar, Cambridge, MA or Becton Dickinson Labware, Lincoln Park, NJ) containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 0.12 to 30 μM.

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (0.12 to 30 μM). The final concentration of PBMC suspension is 1.5–2 X 10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 5-10 minutes at 1000 rpm (~200 x g) at 4°C. The cell-free culture supernatant is removed with a sterile polypropylene pipet and transferred to sterile polypropylene tubes. Samples are maintained at –30 to -70°C until analysis. The samples are analyzed for interferon (α) and for tumor necrosis factor (α) by ELISA

Interferon (α) and Tumor Necrosis Factor (α) Analysis by ELISA

Interferon (α) concentration is determined by ELISA using a Human Multi-Species kit from PBL Biomedical Laboratories, New Brunswick, NJ. Results are expressed in pg/mL.

Tumor necrosis factor (α) concentration is determined using ELISA kits available from Genzyme, Cambridge, MA; R&D Systems, Minneapolis, MN; or Pharmingen, San Diego, CA. Results are expressed in pg/mL.

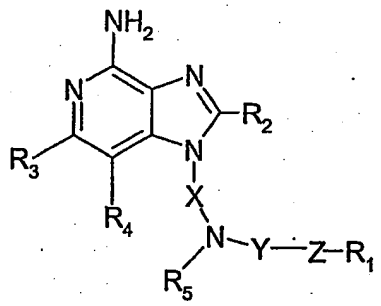
The table below lists the lowest concentration found to induce interferon and the lowest concentration found to induce tumor necrosis factor for each compound. A "*" indicates that no induction was seen at any of the tested concentrations.

Cytokine Induction in Human Cells		
Example Number	Lowest Effective Concentration (μM)	
	Interferon	Tumor Necrosis Factor
1	0.12	1.11
2	0.0046	0.01
3	0.01	0.37
4	0.12	0.37
5	0.01	0.12
6	0.01	0.01
7	0.37	*
8	0.04	10

The present invention has been described with reference to several embodiments thereof. The foregoing detailed description and examples have been provided for clarity of understanding only, and no unnecessary limitations are to be understood therefrom. It will be apparent to those skilled in the art that many changes can be made to the described embodiments without departing from the spirit and scope of the invention. Thus, the scope of the invention should not be limited to the exact details of the compositions and structures described herein, but rather by the language of the claims that follow.

WHAT IS CLAIMED IS:

1. A compound of the formula (I):



(I)

wherein **X** is alkylene or alkenylene;

Y is –CO–, –CS–, or –SO_2–;

Z is a bond, –O–, –S–, or –NR_5–;

R_1 is aryl, heteroaryl, heterocyclyl, C_{1-20} alkyl or C_{2-20} alkenyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of:

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-substituted cycloalkyl;

-O-alkyl;

-O-$(alkyl)_{0-1}$-aryl;

-O-$(alkyl)_{0-1}$-heteroaryl;

-O-$(alkyl)_{0-1}$-heterocyclyl;

-COOH;

-CO-O-alkyl;

-CO-alkyl;

-$S(O)_{0-2}$ -alkyl;

-$S(O)_{0-2}$–(alkyl)$_{0-1}$-aryl;
-$S(O)_{0-2}$–(alkyl)$_{0-1}$-heteroaryl;
-$S(O)_{0-2}$–(alkyl)$_{0-1}$-heterocyclyl;
-(alkyl)$_{0-1}$-N N(R_5)$_2$;
-(alkyl)$_{0-1}$-NR_5-CO-O-alkyl;
-(alkyl)$_{0-1}$-NR_5-CO-alkyl;
-(alkyl)$_{0-1}$-NR_5-CO-aryl;
-(alkyl)$_{0-1}$-NR_5-CO-heteroaryl;
-N_3;
-halogen;
-haloalkyl;
-haloalkoxy;
-CO-haloalkyl;
-CO-haloalkoxy;
-NO_2;
-CN;
-OH;
-SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R_2 is selected from the group consisting of:
-hydrogen;
-alkyl;
-alkenyl;
-alkyl-O-alkyl;
-alkyl-S-alkyl;
-alkyl-O-aryl;
-alkyl-S-aryl:
-alkyl-O- alkenyl;
-alkyl-S- alkenyl; and
-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:
-OH;

-halogen;
-$N(R_5)_2$;
-CO-$N(R_5)_2$;
-CS-$N(R_5)_2$;
-So_2-$N(R_5)_2$;
-NR_5-CO- C_{1-10} alkyl;
-NR_5-CS C_{1-10} alkyl;
-NR_5- So_2- C_{1-10} alkyl;
-CO-C_{1-10} alkyl;
-CO-O-C_{1-10} alkyl;
-N_3;
-aryl;
-heteroaryl;
-heterocyclyl;
-CO-aryl; and
-CO-heteroaryl;

R_3 and R_4 are independently selected from the group consisting of alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio;

each R_5 is independently H or C_{1-10}alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound or salt of claim 1 wherein Y is –CO–.

3. A compound or salt of claim 1 wherein Y is –CO– and Z is a bond.

4. A compound or salt of claim 3 wherein R_1 is alkyl, aryl or substituted aryl.

5. A compound or salt of claim 1 wherein Y is –CS–.

6. A compound or salt of claim 1 wherein Y is –CS– and Z is –NR_5–.

7. A compound or salt of claim 6 wherein R_5 is H and R_1 is aryl or substituted aryl.

8. A compound or salt of claim 1 wherein Y is $-SO_2-$.

9. A compound or salt of claim 1 wherein Y is $-SO_2-$ and Z is a bond.

10. A compound or salt of claim 9 wherein R_1 is alkyl, aryl, or substituted aryl.

11. A compound or salt of claim 10 wherein R_1 is alkyl.

12. A compound or salt of claim 1 wherein Y is $-SO_2-$ and Z is $-NR_5-$.

13. A compound or salt of claim 12 wherein R_5 is alkyl and R_1 is alkyl.

14. A compound or salt of claim 1 wherein R_2 is H, alkyl or alkyl–O–alkyl.

15. A compound or salt of claim1 wherein X is $-(CH_2)_{2-4}-$.

16. A compound or salt of claim 1 wherein R_3 and R_4 are independently H or alkyl.

17. A compound selected from the group consisting of:

N-[4-(4-amino-2-butyl-6,7-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)-butyl]benzamide;

N-[4-(4-amino-2-butyl-6,7-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)-butyl]methanesulfonamide;

N-[4-(4-amino-2-butyl-6,7-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)-butyl]-4-fluorobenzenesulfonamide monohydrate;

N-[4-(4-amino-2-butyl-6,7-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)-butyl]-N'-phenylthiourea monohydrate;

N'-[4-(4-amino-2-butyl-6,7-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)-butyl]-N,N-dimethylsulfamide;

N-[4-(4-amino-2-butyl-6,7-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)-butyl]-N'-phenylurea;

N-[4-(4-amino-2,6,7-trimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]methanesulfonamide;
N-[4-(4-Amino-2-butyl-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-4-[[2-(dimethylamino)ethoxy](phenyl)methyl]benzamide; and
N-{4-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}methanesulfonamide;
or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 in combination with a pharmaceutically acceptable carrier.

19. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 9 in combination with a pharmaceutically acceptable carrier.

20. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 17 in combination with a pharmaceutically acceptable carrier.

21. A method of inducing cytokine biosynthesis in an animal comprising administering a therapeutically effective amount of a compound of claim 1 to the animal.

22. A method of treating a viral disease in an animal comprising administering a therapeutically effective amount of a compound of claim 1 to the animal.

23. A method of treating a neoplastic disease in an animal comprising administering a therapeutically effective amount of a compound of claim 1 to the animal.

24. A method of inducing cytokine biosynthesis in an animal comprising administering a therapeutically effective amount of a compound of claim 9 to the animal.

25. A method of treating a viral disease in an animal comprising administering a therapeutically effective amount of a compound of claim 9 to the animal.

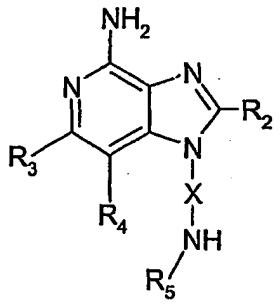
26. A method of treating a neoplastic disease in an animal comprising administering a therapeutically effective amount of a compound of claim 9 to the animal.

27. A method of inducing cytokine biosynthesis in an animal comprising administering a therapeutically effective amount of a compound of claim 17 to the animal.

28. A method of treating a viral disease in an animal comprising administering a therapeutically effective amount of a compound of claim 17 to the animal.

29. A method of treating a neoplastic disease in an animal comprising administering a therapeutically effective amount of a compound of claim 17 to the animal.

30. A compound of the formula (II):



(II)

wherein: **X** is alkylene or alkenylene;

$\mathbf{R_2}$ is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-alkyl-O-alkyl;

-alkyl-S-alkyl;

-alkyl-O-aryl;

-alkyl-S-aryl;

-alkyl-O- alkenyl;

-alkyl-S- alkenyl; and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

-$N(R_5)_2$;

-$CO\text{-}N(R_5)_2$;

-$CS\text{-}N(R_5)_2$;

-$SO_2\text{-}N(R_5)_2$;

-$NR_5\text{-}CO\text{-}C_{1\text{-}10}$ alkyl;

-$NR_5\text{-}CS\text{-}C_{1\text{-}10}$ alkyl;

-$NR_5\text{-}SO_2\text{-}C_{1\text{-}10}$ alkyl;

-$CO\text{-}C_{1\text{-}10}$ alkyl;

-$CO\text{-}O\text{-}C_{1\text{-}10}$ alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

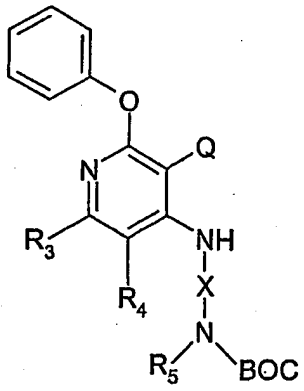
-CO-heteroaryl;

R_3 and R_4 are independently selected from the group consisting of alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio; and

each R_5 is independently H or $C_{1\text{-}10}$ alkyl;

or a pharmaceutically acceptable salt thereof.

31. A compound of the formula (III):



(III)

wherein: Q is NO_2 or NH_2;

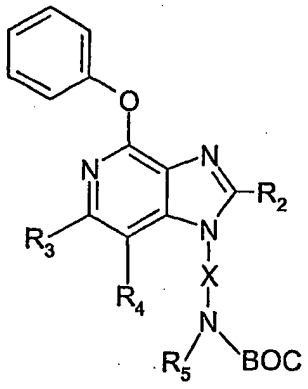
X is alkylene or alkenylene;

R_3 and R_4 are independently selected from the group consisting of alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio; and

R_5 is H or C_{1-10} alkyl;

or a pharmaceutically acceptable salt thereof.

32. A compound of the formula (IV):



(IV)

wherein: X is alkylene or alkenylene;

R_2 is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-alkyl-O-alkyl;

-alkyl-S-alkyl;

-alkyl-O-aryl;

-alkyl-S-aryl;

-alkyl-O- alkenyl;

-alkyl-S- alkenyl; and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

-$N(R_5)_2$;

-$CO\text{-}N(R_5)_2$;

-$CS\text{-}N(R_5)_2$;

-$SO_2\text{-}N(R_5)_2$;

-$NR_5\text{-}CO\text{-}C_{1\text{-}10}$ alkyl;

-$NR_5\text{-}CS\text{-}C_{1\text{-}10}$ alkyl;

-$NR_5\text{-}SO_2\text{-}C_{1\text{-}10}$ alkyl;

-$CO\text{-}C_{1\text{-}10}$ alkyl;

-$CO\text{-}O\text{-}C_{1\text{-}10}$ alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

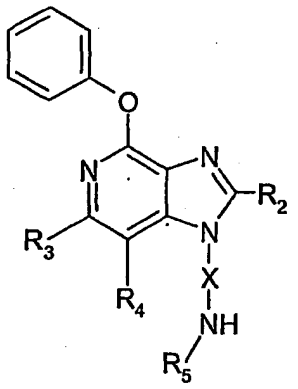
-CO-heteroaryl;

R_3 and R_4 are independently selected from the group consisting of alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio; and

each R_5 is independently H or $C_{1\text{-}10}$ alkyl;

or a pharmaceutically acceptable salt thereof.

33. A compound of the formula (V):



(V)

wherein: X is alkylene or alkenylene;

R_2 is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-alkyl-O-alkyl;

-alkyl-S-alkyl;

-alkyl-O-aryl;

-alkyl-S-aryl;

-alkyl-O-alkenyl;

-alkyl-S-alkenyl; and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

-$N(R_5)_2$;

-$CO\text{-}N(R_5)_2$;

-$CS\text{-}N(R_5)_2$;

$-SO_2-N(R_5)_2$;

$-NR_5-CO-C_{1-10}$ alkyl;

$-NR_5-CS-C_{1-10}$ alkyl;

$-NR_5-SO_2-C_{1-10}$ alkyl;

$-CO-C_{1-10}$ alkyl;

$-CO-O-C_{1-10}$ alkyl;

$-N_3$;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

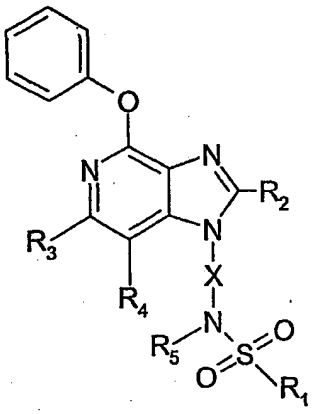
-CO-heteroaryl;

R_3 and R_4 are independently selected from the group consisting of alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio; and

each R_5 is independently H or C_{1-10} alkyl;

or a pharmaceutically acceptable salt thereof.

34. A compound of the formula (VI):



(VI)

wherein: X is alkylene or alkenylene;

R_1 is aryl, heteroaryl, heterocyclyl, C_{1-20} alkyl or

C_{2-20} alkenyl, each of which may be unsubstituted or substituted by one or more substituents independently selected from the group consisting of:

-alkyl;
-alkenyl;
-aryl;
-heteroaryl;
-heterocyclyl;
-substituted cycloalkyl;
-O-alkyl;
-O-$(alkyl)_{0-1}$-aryl;
-O-$(alkyl)_{0-1}$-heteroaryl;
-O-$(alkyl)_{0-1}$-heterocyclyl;
-COOH;
-CO-O-alkyl;
-CO-alkyl;
-$S(O)_{0-2}$-alkyl;
-$S(O)_{0-2}$-$(alkyl)_{0-1}$-aryl;
-$S(O)_{0-2}$-$(alkyl)_{0-1}$-heteroaryl;
-$S(O)_{0-2}$-$(alkyl)_{0-1}$-heterocyclyl;
-$(alkyl)_{0-1}$-$N(R_5)_2$;
-$(alkyl)_{0-1}$-NR_5-CO-O-alkyl;
-$(alkyl)_{0-1}$-NR_5-CO-alkyl;
-$(alkyl)_{0-1}$-NR_5-CO-aryl;
-$(alkyl)_{0-1}$-NR_5-CO-heteroaryl;
-N_3;
-halogen;
-haloalkyl;
-haloalkoxy;
-CO-haloalkyl;
-CO-haloalkoxy;
-NO_2;
-CN;

-OH;

-SH; and in the case of alkyl, alkenyl, and heterocyclyl, oxo;

R_2 is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-alkyl-O-alkyl;

-alkyl-S-alkyl;

-alkyl-O-aryl;

-alkyl-S-aryl;

-alkyl-O- alkenyl;

-alkyl-S- alkenyl; and

-alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

-$N(R_5)_2$;

-$CO\text{-}N(R_5)_2$;

-$CS\text{-}N(R_5)_2$;

-$SO_2\text{-}N(R_5)_2$;

-$NR_5\text{-}CO\text{-}C_{1\text{-}10}$ alkyl;

-$NR_5\text{-}CS\text{-}C_{1\text{-}10}$ alkyl;

-$NR_5\text{-}SO_2\text{-}C_{1\text{-}10}$ alkyl;

-$CO\text{-}C_{1\text{-}10}$ alkyl;

-$CO\text{-}O\text{-}C_{1\text{-}10}$ alkyl;

-N_3;

-aryl;

-heteroaryl;

-heterocyclyl;

-CO-aryl; and

-CO-heteroaryl;

R_3 and R_4 are independently selected from the group consisting of alkyl, alkenyl, halogen, alkoxy, amino, alkylamino, dialkylamino and alkylthio; and

each R_5 is independently H or C_{1-10} alkyl;

or a pharmaceutically acceptable salt thereof.

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(71) Applicant: 3M INNOVATIVE PROPERTIES COMPANY [US/US]; 3M Center, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

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(74) Agents: HOWARD, MarySusan et al.; Office of Intellectual Property Counsel, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK (utility model), SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

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WO 02/046194 A3

(54) Title: SUBSTITUTED IMIDAZOPYRIDINES

(57) Abstract: Imidazopyridine compounds that contain substituted amine functionality at the 1-position are useful as immune response modifiers. The compounds and compositions of the invention can induce the biosynthesis of various cytokines and are useful in the treatment of a variety of conditions including viral diseases and neoplastic diseases.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/46915

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61K31/437 A61P31/12 A61P35/00
//(C07D471/04,235:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 29693 A (MINNESOTA MINING & MFG) 17 June 1999 (1999-06-17) claims 1,10,15-20; examples 45-213	1-34
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Y	US 5 494 916 A (LINDSTROM KYLE J ET AL) 27 February 1996 (1996-02-27) cited in the application column 7, line 58 -column 8, line 5; claims 1,10,11	1-34

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 September 2002	25/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 268 376 A (GERSTER JOHN F) 7 December 1993 (1993-12-07) cited in the application schemes I, II, III column 11, line 6 - line 45; claims 1,10	1,18-34
A	US 4 929 624 A (GERSTER JOHN F ET AL) 29 May 1990 (1990-05-29) cited in the application columns 3, 4, reaction scheme column 6, line 21 -column 7, line 16; claims 1,4-6	1,18-34
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A	US 5 389 640 A (GERSTER JOHN F ET AL) 14 February 1995 (1995-02-14) cited in the application columns 7-10, reaction scheme column 11, line 51 - line 68; claim 1	1,18-34
A,P	WO 00 76519 A (3M INNOVATIVE PROPERTIES CO) 21 December 2000 (2000-12-21) cited in the application page 8 -page 13; claims; examples	1-34
A,P	& WO 00 76518 A 21 December 2000 (2000-12-21) cited in the application	
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/46915

Box I Observations where certain claims w re found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 21-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[] The additional search fees were accompanied by the applicant's protest.

[] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/US 01/46915

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